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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,835	MATSUDA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,30,32-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *1-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32-37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09-15-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 09-15-2008 has been entered.
3. Status of claims. Claims 1-26, 30, 32-37 and 39-40 are pending. Claims 30 and 39 have been amended, and claims 31 and 38 have been canceled by Applicants' amendment filed on 09-15-2008. Claims 1-26 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention. The election was made **without traverse** in Applicants' responses filed on in the replies filed on 11-05-2007 and 03-06-2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
4. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Keigo Hanada. Note that all the statements of the declaration which are discussed at pages 3-5 of the Remarks filed on 09-15-2008, are addressed in the response to Applicants' arguments by the examiner.
5. Therefore claims 30, 32-37 and 39-40 are currently being examined to which the following grounds of rejection are applicable.

Response to arguments

Withdrawn objection/ rejections in response to Applicant arguments or amendments:

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 09-15-2008 is in compliance with the provisions of 37 CFR 1.97. The following references have been considered by the examiner, as indicated on Form PTO 1449.

a) Reference AL, Maymi et al., has been considered to the extent that an English translation of the relevant portions of the document has been provided.
b) Reference AM, Ikada et al., has been considered to the extent that an English translation of the relevant portions of the document has been provided.
c) Reference AO, Yamaoka et al., has been considered to the extent that an English translation of the relevant portions of the document has been provided.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) by checking boxes 12(a)(1) on the coversheet.

Objections to the Specification

In view of applicants' amendment of the specification at page 9, lines 23-24 and lines 27-29; page 12, lines 18-22, lines 23-28, the objection to the specification has been withdrawn.

Objections/rejection maintained in response to Applicants' arguments or amendments.

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

Claims 30, 32-37 and 39-40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting growth, invasion and metastasis of cancer or for inhibiting angiogenesis, which comprises administering a cell-

containing preparation comprising a cell which has a DNA as set forth in SEQ ID NO:2, which encodes a mature human NK4 polypeptide, does not reasonably provide enablement for other fragments or variants thereof which encode a protein which has an activity equivalent to NK4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Response to Applicants' arguments as they apply to rejection of 30, 32-37 and 39-40 remain rejected under 35 U.S.C. 112, first paragraph.

At page 10 of remarks, Applicants essentially argue that the skilled artisan would obtain any of the fragments and/or variants of SEQ ID NO:2, which encodes a mature human NK4 polypeptide, as embraced by amended claim 1 without undue experimentation by the hybridization methods disclosed in the specification as filed. Such is not persuasive.

The breadth of the claim 30 encompasses fragments and variants of SEQ ID No. 2, which encodes a mature human NK4 polypeptide. As stated at pages 7-8 in the previous office action filed on 06-13-2008, hybridization of two nucleic acids, even under high stringency conditions, requires only that the two nucleic acids share between 25 and 50 nucleotides in common. The specification does not disclose regions or domains of the protein of SEQ ID No. 4 encoded by the nucleotide of SEQ ID No. 2 that are essential for the claimed activity i.e., the peptide has an antagonist activity against hepatocyte growth factor (HGF) and an inhibitory action against angiogenesis. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. Since it would require undue experimentation to identify other fragments and/or variants of a polypeptide of SEQ ID No. 4, it certainty would require

undue experimentation to make and use the invention as claimed. Neither prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of claimed fragments and/or variants of SEQ ID No. 2 encoding SEQ ID No. 4, i.e. the mature polypeptide NK4 wherein the coding sequence for amino acids 131-135 of the SEQ ID No. 3 are deleted.

Claim Rejections - 35 USC § 103

The instant claims are drawn to a method for inhibiting growth and metastasis of cancer cells in a mammal by administration of a cell-containing preparation comprising cells containing a DNA having a base sequence of SEQ ID NO: 2, which encodes a mature NK4 polypeptide fragment of HGF or any DNA sequence fragment able to hybridize under stringent conditions to SEQ ID NO: 2, a fibrous protein and a mesh sheet comprising a biodegradable resin, the cell being an epithelial cell. A DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 2 under stringent condition is broadly interpreted as any DNA fragment sequences that hybridize to any portion of SEQ ID No. 2 , for example, a base sequence that comprises a sequence complementary to SEQ ID No. 1.

To the extent that claim 20 reads on **"the cell being … a fibroblast", the following rejections are maintained.**

Claims **30, 32 and 34-37 and 39** remain rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-

327, 1990; hereafter Seki-A) for the reasons already of record and the reasons set forth in the following paragraphs.

In addition to the teaching of Folkman et al., Kuba et al. Nakamura, T., (EP 1074264), Nakamura, T., and Seki et al. disclosed in the Office action of 06-13-2008, Folkman et al., teaches transformation of various cells including epidermal cells (col. 15, line 7) and treatment of accumulation of fibroblasts, i.e. fibroplasias (col. 6, line 16). Folkman et al., also teaches that cells are transfected with a recombinant DNA molecule comprising an angiostatin DNA sequence capable of expressing angiostatin(col. 17 lines 12-15) (Current **claim 37**). Furthermore, Nakamura exemplifies transformation of CHO cells which are fibroblasts with human HGF cDNA (EP, col. 12, lines 45-55, Example 1) (**Current claim 20, in part**).

Response to Applicants' arguments as they apply to rejection of claims 30, 32, 34-37, 39 under 35 USC § 103

At page 11 of remarks Applicants traverse the rejection of claims 30, 32, 34-37, 39 and 40 alleging essentially that Folkman teaches combination of proteins are combined with biodegradable polymers such as collagen whereas the instant claims required that the cells are combined with a fibrous protein. Moreover, Applicants argue that the biodegradable polymer of Folkman serves as a sustained-release compound whereas the fibrous protein claimed by the invention serves as a carrier of the cells. Such is not persuasive.

As set forth at page 10 of the previous office action, Folkman et al., clearly teaches *ex vivo* transformed cells in combinations with therapeutic compositions such as a collagen matrix (col. 21; lines 17, 20 and 28). Note that collagen is a fibrous protein as supported by the disclosure of the instant invention. As both Folkman and the instant invention teach collagen

matrices that are biodegradable combined with transduced cells, any functional property (e.g., sustained-release, maintaining strength of the cell-containing preparation) resulting from the claimed transformed cell compositions comprising the fibrous protein and biodegradable matrix is inherently anticipated because the structural limitations of the fibrous protein and the biodegradable matrix are the same.

At page 12 of Remarks, Applicants essentiality argue that the fibrous protein claimed by the invention includes a culture medium so nutrients can be supplied to the cells-containing preparation, leading to stable and longer survival of the cell when administered to the living body. Moreover, Applicants refer to Figure 1 of the application, allegedly providing support for a mesh sheet that allows cells to be release in the opposite direction of the sheet to be efficiently delivered to the target site. Such is not persuasive.

With respect to applicants' argument that, "the mesh sheet maintains strength of the cell-containing preparation, although the fibrous protein comprising a culture medium suitable for culturing cells (see page 12)," is not found persuasive because it is noted that the features upon which applicant relies (i.e., the fibrous protein used in the present invention to contain components of a culture medium suitable for culturing the cells of the invention, Specification page 12, lines 26-27) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite the fibrous protein comprising components of a culture medium taught in the specification. Furthermore, in relation to Fig. 1, the specification merely discloses that the cell layer structure permits the cell-containing layer to directly contact the administration site so that

NK4 secreted from the cells can be efficiently supplied to the cancer cells (p. 24, lines 14-17). This is in contrast to Applicants arguments about an opposite directional release to the mesh sheet.

In relation to the Medico reference, Applicants essentially contend that, in contrast to the Medico reference suggesting epithelial cells as target of HGF, the instant invention requires the epithelial cell of the oral mucosa to release NK4. In addition, at page 13 of remarks, Applicants list the four advantages of using epithelial cells. Hence Applicants argue that Medico does not teach nor suggest releasing NK4, thereby providing the advantages of using epithelial cells listed by Applicants. Such is not persuasive.

Folkman teaches therapeutic cell compositions for treating cancer comprising a base sequence encoding NK4 and various cells transformed including epidermal cells, which comprise epithelial cells (see Junqueira, p. 64, col. 1, paragraph 4). Medico discloses that epithelial cells are target of NK4, because epithelial cell comprise the Met tyrosine kinase/HGF receptor to mediate biological responses including cell proliferation. It would have been obvious for the skill artisan to use epithelial cells in the method taught by the combined references of Folkman, Kuba and Nakamura in order to reduce or inhibit epithelial cell proliferation by expressing NK4 in a therapeutic cell composition. This is because human NK4 protein functions as an anti-tumor agent because of its antagonism to the c-Met/HGF receptor which is a function independent of its anti-angiogenic activity. Indeed, Kuba teaches that blockage of the c-Met/HGF receptor was responsible for the inhibition of metastasis by NK4 administration. In response to applicant's argument that “These advantages of cell-containing preparation comprising a fibrous protein and a mesh sheet and advantages of using an epithelial cell of the

oral mucosa or a fibroblast are shown in declaration attached hereto", the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Claim 33 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., EP 1074264, Nakamura, T., WO 99/55361 and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims **30, 32 and 34-37 and 39** above and further in view of Allen et al., (US Patent 7,115,256; Date of Patent, Oct. 3, 2006) for the reasons already of record and the reasons set forth in the paragraphs above.

Claim 33 remains rejected for the reasons already of record and the reasons set forth in the paragraphs above. Note that Applicant has provided a single response that properly applies to the rejection of claims 30, 32, 34-37, 39 under 35 USC § 103, claim 33 under 35 USC § 103, and claim 40 under 35 USC § 103 and is equally relevant.

To the extent that claims 30 and 40 read on epithelial cells of the oral mucosa, claims 30 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) as

applied to claims **30, 32 and 34-37 and 39** above, and further in view of Medico et al., , US Patent US 6551991 (Date of Patent, April 22, 2003) and Junqueira et al., (Basic Histology, 1986, Lange Medical Publications, pp. 64-65).

Claims 30 and 40 reading on epithelial cells of the oral mucosa remain rejected for the reasons already of record and the reasons set forth in the paragraphs above. Note that Applicant has provided a single response that properly applies to the rejection of claims 30, 32, 34-37, 39 under 35 USC § 103, claim 33 under 35 USC § 103 and claim 40 under 35 USC § 103, and is equally relevant.

Response to Amendment

The declaration under 37 C.F.R. § 1.132 signed by Dr. Keigo Hanada, filed on 09-15-2008 is insufficient to overcome the rejection of claims 30, 32-37 and 39-40 based upon the properties of the fibrous protein comprising culture medium, the mesh sheet maintaining strength of the cell-containing preparation and, further, the advantages of using epithelial cells of the oral mucosa in cell-containing preparation, for the reasons set forth in the last Office action and the reasons set forth in the paragraphs above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 37 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 30. Claim 37 recites: "the cell-containing preparation is capable of forming a peptide encoded by a DNA having the sequence represented by SEQ ID NO:2 ". However, claim 30 already recites "administering a cell-containing preparation comprising a cell with has a DNA having a base sequence represented by SEQ ID NO:2 … encoding a protein which has the activity equivalent to NK4", which has the same scope of the limitation "the cell-containing preparation is capable of forming a peptide encoded by a DNA having the sequence represented by SEQ ID NO:2" as recited in claim 37. Therefore, claim 37 does not differ in scope from claim 30. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

Claims 30, 32-37 and 39-40 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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